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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/764,390	RAITANO ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *49,54,56-58,63,66,72,75,77,79 and 80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *49,54,56-58,63,66,72,75,77,79 and 80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/28/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 55 and 59-62 have been canceled. Claims 54, 75, 77, 79 and 80 have been amended. Claims 49, 54, 56-58, 63, 66, 72, 75, 77, 79 and 80 are pending and under consideration.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49, 54-63, 66, 72, 75, 77, 79 and 80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

(A)As drawn to SEQ ID NO:3, 5 and 7, and a method of detecting the presence of cancer in an individual.

Claims 49 and 57 are drawn to an isolated or recombinant polypeptide comprising SEQ ID NO:3, 5 or 7, and composition thereof. Claims 75 and 77 are drawn to a method of detecting cancer in a patient comprising determining the expression level of a polypeptide comprising SEQ ID NO:3, 5 or 7. Claims 54 and 56 are drawn to a polypeptide consisting of nine, ten or fifteen contiguous amino acids of SEQ ID NO:3, 5 or 7 wherein the peptide induces a specific antibody response against a polypeptide having SEQ ID NO:3, 5 or 7. The specification asserts that 254P1D6B can be used in the same manner as other tumor antigens such as PSA, because 254P1D6B is expressed in lung, ovary, prostate, pancreas and breast tissues, when said tissues are malignant (page 122). The specification sets forth the polynucleotide of 254P1D6B v.1 clone LCP-3 as encoding SEQ ID NO:3 (Figure 2A); polynucleotides of 254P1D6B v.2 as encoding SEQ ID NO:5 (Figure 2B) and 254P1D6B v.3 as encoding SEQ ID NO:7 (Figure 2C). The specification fails to provide a nexus between the expression of 254P1D6B in cancerous lung,

ovary, prostate, pancreas and breast and the expression of the individual variant sequences. It is further noted that claim 75 is broadly drawn to accommodate all cancers, rather than the specific cancer listed on page 12 of the specification. When given the broadest reasonable interpretation the term "cancer" includes malignancies from other cell types than those listed on page 122 and in addition includes sarcomas, neuroblastoma, melanomas, leukemias and lymphomas, etc. The scope of the claims must be commensurate with the scope of the enablement set forth. One of skill in the art would be forced into determining if the expression pattern of the claimed variant polynucleotides were the same as that which is set forth for 254P1D6B before being able to use said variants as markers for the detection of the described cancers on page 122, and would be subject to an even greater degree of undue experimentation in order to determine if the polynucleotides of SEQ ID NO:3, 5 and 7 were over expressed in cancers other then those listed on page 122 in order to practice the claimed method to the full scope.. There is no objective evidence that all the variants possess the same properties as that reported for the "generic" 254P1D6B sequence and there is no objective evidence that the "generic" 254P1D6B sequence is over expressed in cancers from various malignancies such as sarcomas, melanomas and neuroblastoma, etc. Further, there are not teachings for how to use the polypeptide of claims 54 and 56 if said peptides do not generate an antibody which binds a polypeptide associated with a cancerous state.

Applicant argues that the amendment of claim 75 to specify that the cancerous tissues which are being examined express the 254P1D6B protein. This is not persuasive. The claims are rejected for lacking enablement because there is no nexus between the expression of the 254P1D6B protein in cancerous tissues such as lung, ovary, prostate, pancreas and breast tissues, (page 122) and the expression of individual clones of v.1, 2, and 3 which are SEQ ID NO:3, 5 and 7. One of skill in the art would still be forced into determining the expression pattern of each said SEQ ID NO:3, 5 and 7 before said variant clones could be used as markers for a cancerous state for the reasons set forth above. It is noted that no data is provided for the expression of the individual SEQ ID NO:3, 5 and 7 in cancerous tissues

Applicant argues that the specification as filed contains Northern blot and PCR data regarding the gene of interest. Applicant is again reminded that the sequence in question are the

variant clone sequence of SEQ ID NO:3, 5, and 7 and there is no data to support the claim to a specific expression pattern for any of SEQ ID NO:3, 5 or 7.

(B)As drawn to a method of generating an immune response.

Claims 58-62, 79 and 80 are drawn to a method of generating an immune response in a mammal comprising exposing cells of said mammal to a polypeptide comprising SEQ ID NO:3, 5 or 7 and encompasses the generation of cytotoxic T cells which kill autologous cells which express said proteins. The specification assets that 254P1D6B is a target for antibody based therapy and contemplates that the antibodies can be used to evoke complement and ADCC-mediated cell killing (page 49). However, it is well known in the art that the antibody must bind to the cell surface in order to evoke complement lysis or ADCC (Abbas et al, "Cellular and Molecular Immunology", 1991, pages 57-58) and there is no evidence in the specification that said 254P1D6B protein is a cell surface protein. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to use the claimed method of generating an immune response wherein said immune response were complement-mediated killing or ADCC. The specification also asserts that intracellular molecules can be targeted by intrabodes. However the specification is not enabled for the making and using of intrabodies for the targeting of the 254P1D6 protein. The art recognizes that in order to provide "intrabodes" it is necessary to known the minimum sequence of an antigen binding portion of an antibody which binds to the protein being targeted (Jones et al., Advanced Drug Delivery Reviews 1998, page 154, column 1, lines18-26, and page 160, lines 24-25). In the instant case no sequence of an antibody has been provided.

The specification asserts that 254P1D6B is a target for cellular immune responses (page 52 and section X.C.). However, the art teaches that the induction of a cellular immune response against a tumor antigen is unreliable. The prior art teaches that tumor cells are phenotypically less stable than normal cells and can escape the immune response of the host by many mechanisms including deficient antigen processing by tumor cells, production of inhibitory substances such as cytokines, tolerance induction, rapidly growing cells which can overwhelm a slower immune response, failure of the host to respond to an antigen due to immunosuppression, tumor burden, infections or age, deficient antigen presentation with the host and failure of the host effector cells to reach the tumor due to the stromal barrier (Paul, Fundamental Immunology,

(text), 1993, page 1163, second column, first sentence under the heading "Factors Limiting Effective Tumor Immunity" and Table 4). Paul teaches that lymphocytes from tumor bearing patients have frequently been found to be cytotoxic to their own tumor cells in vitro, but that this effect was blocked by the addition of sera from said patients. Paul teaches that the constituent of the sera which caused the blocking of the cytotoxicity was unknown, but that antibodies, antibody-antigen complexes and shed antigen have all been implicated in the blocking phenomenon (Paul page 1167, second paragraph under the heading "Immunological Enhancement and Blocking Factors"). Paul also notes that in some cases, immune response to a tumor antigen may sometimes stimulate the growth of the tumor cells directly (last line under the heading "Immunological Enhancement and Blocking Factors", page 1167). With respect to the blocking factor found in serum, Apostolopoulos et al (Nature Medicine, 1998, vol. 4, pp. 315-320) teach that endogenous antibodies present at the time of administration of a tumor peptide re-routes the immune response from a cellular response to a humoral response. In preclinical experiments with mice, MUC1 peptides targeted to the mannose receptor produce high levels of CTL and a low level of antibodies. However, in human clinical trials a low level of CTL and a high level of humoral response was observed (Apostolopoulos, page 315, first column, bridging paragraph). Apostolopoulos et al teach that the presence of endogenous antibodies which bind to the MUC1 peptide was responsible for this re-routing of the immune response from cellular to humoral due to the Fc portion of the antibody (page 319, first column, lines 7-10). Apostolopoulos et al teach that mice are devoid of these antibodies (page 315, second column, lines 9-13) and are thus able to effectively mount a cellular immune response against the target antigen. Apostolopoulos et al teach that these findings have implication for other immunotherapy approaches (page 318, lines 4-8, under the heading "Discussion". In support of these conclusions Jager et al (PNAS, 2000, Vol. 97, pp. 12198-12203) teach that patients who do not have antibodies to the cancer testis antigen, NY-ESO-1, were able to generate a specific T-cell response to NY-ESO after intradermal administration, whereas patients having antibodies prior to treatment which reacted with said antigen already had T-cells which reacted with target cells expressing said antigen in vitro, and said positive patients did not develop significant CTL in response to the administered NY-ESO antigen. These references serve to demonstrate that the

induction of a anti-tumor CTL response after the administration of a tumor peptide is unpredictable.

Paul (ibid) states that deficient antigen presentation is a mechanism by which tumor cells escape immune detection. This is corroborated by the observations set forth in the abstract of Semino et al (Journal of Biological Regulators and Homeostatic Agents, 1993, Vol. 7, pp. 99-105 and the abstract of Algarra et al International Journal of Clinical and Laboratory Research, 1997, Vol. 27, pp. 95-102) which all teach that primary tumors in situ are often heterogeneous with respect to MHC presentation. The effect of the claimed method upon such a heterogeneous tumor has not been demonstrated by the specification. More currently, the abstract of Bodey et al (Anticancer Research, 2000 Jul-Aug, Vol. 20, pp. 2665-2676) teaches that the failure of methods of treating cancer comprising the administration of tumor antigens is due to the failure of cancer vaccines to eliminate the most dangerous cells within a tumor which are so de-differentiated that they no longer express cancer cell specific molecules.

Sarma et al (Journal of Experimental Medicine, 1999, Vol. 189, pp. 811-820) states that a critical issue in therapeutic regiments comprising the administration of tumor antigens for immunotherapy is whether unmutated tumor antigens which are expressed in normal cells impose special restrictions on the CTL response in vivo. Using transgenic mice wherein the antigen specific T cells specific for the P1A non-mutated tumor antigen are expressed at high levels and remain responsive to the P1A antigen when assayed in vitro, it was found that P1A antigen expressed in the thymus resulted in clonal deletion of said specific T-cells Sarma et al note that although said transgenic mice produce an overwhelming majority of T cells that are specific for P1A, said mice are no more resistant to cells expressing P1A than non-transgenic litter mates. Sarma et al concludes that even thought P1A can be a tumor rejection antigen, the effector function of P1A specific CTL is restrained in vivo and that these results have important implications for the strategy of tumor immunotherapy. The specification asserts that the instant tumor antigen is akin to PSA, but does not provide evidence that the 254P1DB protein is a self protein which is differentially up regulated in cancer cells or a mutated protein. Following the pattern of PSA as suggested by the specification would lead to the conclusion that the 254P1DB protein is a self protein which is differentially up regulated in cancer cells and subject to the difficulties associated with a self antigen as those discussed by Sarma above.

It is also well known that the presence or induction of CTL which can lyse target cells in vitro has no apparent nexus with anti-tumor cytolytic activity in vivo. Ohlen et al (Journal of Immunology, 2001, Vol.166, pp. 2863-2870) teach that T-cells recognizing normal proteins expressed in tumors can be isolated in vitro, but that the existence of said T-cells does not preclude in vivo anergy induction and deletion (page 2863, second column, lines 1-6 of the last paragraph). Antoinia et al (International Immunology, 1995, Vol. 7, pp. 715-725) teach that T-cells which are impaired in the ability to proliferate in response to antigen and unable to reject tumors in vivo were fully functional as CTL lymphocytes in vivo (page 724, first column, first full paragraph). These references serve to demonstrate that the induction of a CTL response against the 254P1DB protein ex vivo or in vitro does not constitute evidence that said T-lymphocytes would be effective at lysing tumor cells in vivo or functioning in immunotherapy in a patient in need thereof.

Further, it is recognized in the art that animal models for immunotherapy are deficient. Schultze et al (Trends in Immunology, 2004, Vol. 25, pp 659-664) teach that encouraging animal model studies lead to clinical trails, but that the general outcomes of these trials are disappointing, citing a discrepancy between the outcome of pre-clinical models and the outcome of the human situation. Bodey et al, (Anticancer Research, 2000, Vol. 20, pp. 2665-2676) teach that the animal models often produce highly encouraging results but that the resulting response in humans is disappointing

It is concluded based on the references discussed above, that the state of the art with respect to treating patients with cancer by means of administering tumor antigens is unpredictable. The specification does not provide any disclosure that the administration of the claimed polypeptides would generate CTLs which lyse the cells of a tumor in situ, and it cannot be predicted based on the prediction of HLA-binding motifs that said polypeptides would be useful in immunotherapy in patients. Thus, without a demonstration that the administration of the claimed polypeptides or cells expressing said polypeptides overcomes immunosuppression of the host, the rapid growth of the target tumor cells, failure to access the tumor because of the stromal barrier and tolerance induction in the host and objective evidence that the target tumor cells in vivo present adequate tumor rejection antigen on the surface of all the tumor cells, one of

skill in the art would be subject to undue experimentation without reasonable expectation of success in order to use the claimed method of treatment and the claimed polypeptides.

Applicant argues against the reference of Abbas stating that Abbas does not explicitly recite the need for the antibody to bind to the cell surface. This has been considered but not found persuasive. The alternative to binding a cell on the surface is binding a cell at a non-surface epitope. In order for an antibody to bind to a cell at a non-surface epitope the cell must be chemically or physically permeabilized to allow access to non-surface epitopes. A cell within an organisms has not been permeabilized, therefore the antibody by default is binding an epitope of the surface. Further, column 1, lines 2-3 of Abbas refer to the binding and coating of antigenic particles. To "coat" is commensurate with binding on the surface.

(D)As drawn to the expression analysis of 254P1D6B and the individual sequences of SEQ ID NO:2, 4 or 6.

Claims 63, 66 and 72 are drawn to the polynucleotides encoding the polypeptides of SEQ ID NO3, 5 or 7, full complements thereof; and polynucleotides comprising SEQ ID NO:2, 4 and 6. The polynucleotides sequences are rejected for the same reasons as applied to the polypeptides in section (A) above.

Applicant again argues that actual data has been presented to allow a nexus between the polynucleotides and the detection of cancer. As stated above, no specific data has been presented for the individual sequences of SEQ ID NO:2, 4 and 6, or the polypeptides encoded therefrom.

The rejection of claims 54-56 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 54 has been amended to recite wherein the fragment consists of nine, ten or fifteen contiguous amino acids of the polypeptide of claim 49, and wherein said fragment induces a specific antibody response. It is noted that the tables on pages 136-196 provide numerous examples of fragment having nine, ten or fifteen contiguous amino acids of the polypeptides of claim 49, however, the specification

lacks specific support for this limitation in combination with the induction of a specific antibody response. One of skill in the art would reasonable conclude that applicant was not in possession of the claimed genus of fragments.

Applicant argues that what has not been literally described was conventionally known in the art. this has been considered but not found persuasive because neither the polypeptides of SEQ ID NO:3, 5 or 7 or the fragments of said polypeptides which provide an antibody response against SEQ ID NO:3, 5 and 7 are conventionally known in the art, therefore the connection between the epitopes and the induction of a specific antibody response cannot be inferred from the prior art.

All other rejections and objections as se forth or maintained in the previous Office action are withdrawn.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.
3/3/2007